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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,990	BRAHMBHATT ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009 and 11 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/2010,10/29/09, 4/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to notice of non compliant amendments to the claims filed January 11, 2010 has been entered. It is noted that the notice of non compliant amendments to the claim was inadvertently mailed because of examination of a prior version of the claim that was not entered during international phase. Therefore, amendments to the claims filed 9/17/2009 have been entered. Applicants have amended claims 1-10, 12-18, while claims 11, 19-35 have been canceled. Currently, claims 1-10, 12-18 are pending.

Election/Restrictions

Applicants' election of claims 1-18 and 35 (Group I) in the reply filed on December 15, 2008 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-10, 12-18 are under current examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 4/13/2009, 10/29/2009 and 1/23/2010 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Withdrawn-Claim Objections

Applicants' arguments that claim 18 has been amended to end with a period and begin with an article "the" are persuasive, therefore objection to 2-18 are hereby withdrawn. Applicants' cancellation of claim 35 renders its objection moot.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 35 were rejected under 35 U.S.C. 112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants' cancellation of claims 11 and 35 renders their rejections moot. In view of applicants' amendments to the claim, the rejection set forth on pp. 4-13 of the previous office action dated March 19, 2009 is hereby withdrawn.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7-11, 13-18 remain rejected under 35 U.S.C. 102(e) as being anticipated by Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002) for the reasons of record.

Claims are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Subsequent claims limit the method of 1 wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor. Claims further limit the method according to base, wherein mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicells. Claim 9 limits the bispecific ligand of claim 1 to include an antibody or antibody fragment. Claim 11 limits the minicells of claim 1 to an intact cell wall. Claims 14 and 15 limit the method wherein mammalian cells are under *in vitro* or *in vivo* condition. Claim 35 is included in the rejection because of the breadth of the claims. The

rejection is applied to the extent method only requires administering minicells containing a therapeutic nucleic acid and a bispecific ligand that is capable of binding minicells and target non phagocytic mammalian cell. The rejection is not to a method of treating a disease or modifying trait. It is noted that specification teaches useful ligands include receptors, enzymes, binding peptides, fusion/chimeric proteins and small molecules. The bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively.

With respect to claims 1-4, 7-9, Sabbadini et al. teach a gene delivery method comprising contacting a mammalian cell with a bacterial minicells comprising a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. Sabbadini teaches that the active agent is a nucleic acid (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66) and the target mammalian cell may include cos or A-431 cancer cell line that are non phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37). The compound to be conjugated to the minicells can be a polypeptide or a lipid. It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Furthermore, Sabbadini et al teach attaching compounds-or moieties to minicells via membrane proteins that are displayed on the minicells (see col.4 and 5). Thus, the antibody displayed on the surface of the minicell attaches to cell surface receptor would be monospecific to first and second arm respectively. It is also disclosed that the minicells containing genetic material targets cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18) meeting the limitation of claims 1-4, 7-9. Additionally, Sabbadini et al teach that the antibody may be a single chain antibody (see col. 132, line 60) or a humanized antibody (col. 132, line 53) (limitation of claim 10). With respect to claim 11, Sabbadini et al disclose that the minicells produced contains an intact cell wall (see col. 39, lines 34-35, and claims 1, 8 in '105). Regarding claims 12-13, Sabbadini et al contemplates a method to deliver expression plasmids that could correct protein expression deficiencies or abnormalities as in cystic fibrosis by delivering nucleic acid encoding chloride channel (see col. 167, lines 35) or DNA to kill the cell (see col. 38, line 13). Sabbadini et al. also teach that minicells may also be use to deliver antisense oligonucleotide to the target cell (see column 167, lines 20-23). With respect to claims 14-15, Sabbadini et al. teach that method of gene transfer that may occur between minicells and a mammalian cell under *in vitro* or *in vivo* condition (see col. 251, lines 40-43). Regarding claims 16-18, Sabbadini et al. teaches minicells comprising first and second nucleic acids and wherein each nucleic acid comprises expression sequences (see columns 25, lines 4-14). Sabbadini et al. disclose that nucleic acids of the invention can be delivered by minicells containing plasmids or expression vectors comprising sequences encoding the nucleic acids, wherein the expression constructs comprise regulatory elements operably linked to a nucleotide sequence that serves as a template for a bioactive nucleic acid (see column 17 and example 19). Sabbadini et al. teach that a minicell of the

invention comprises at least one nucleic acid, wherein the nucleic acid comprises an expression construct comprising expression sequences operably linked to an ORF encoding a protein (see column 23, line 48-52, column 24, lines 1-3). Sabbadini et al. teach plasmid pMPX-6 comprising nucleic acid encoding reporter protein (EGFP) under the control of CMV promoter to monitor the efficiency of gene transfer (example 19). With respect to claim 35, Sabbadini et al teach administering minicells containing genetic material to target host mammalian cells (col. 159 lines 4-6, column 167, lines 30-45).

Accordingly, Sabbadini et al anticipates claims 1-4, 7-18 and 35.

Response to arguments

Applicant arguments filed September 17, 2009 have been fully considered but are found not persuasive. Applicants' cancellation of claims 11 and 35 renders their rejections moot. Applicants disagree with the rejection of claims and argue that Sabbadini present broad genus of cell types, including eubacterial minicell, eukaryotic minicell and anchebacterial minicell and characterization of minicell as useful for delivering "genus of therapeutic agents" including small molecule, polypeptide, antibodies, nucleic acid and drugs . Applicants assert that Sabbadini do not delineate "targeted gene delivery method, bispecific ligand having specificity for a mammalian cell surface receptor capable of activating receptor-mediated endocytosis" (see pages 5 and 6 of the arguments).

Applicants' arguments have been fully considered, but are not found persuasive. As an initial matter, base claim is directed to a targeted gene delivery method that involves one active method step comprising bringing bispecific ligands having specificity for a mammalian cell surface receptor capable of activating receptor mediated endoytosis into contact with (a) intact bacterially derived minicell that contains nucleic acid operably linked to a promoter and (b) non-phagocytic mammalian cell. Contrary to applicant's arguments that disclosure of Sabbadini et al is cherry picking elements from a laundry list, it is noted that Sabbadini et al. specifically teaches the method of bringing a target non-phagocytic mammalian cell with a minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of the target mammalian cell, wherein the bacterially derived intact minicell comprises a nucleic acid, wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66). It is also disclosed that the

receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37). Applicant should further note that Sabbadini et al specifically teach using bacterially derived intact minicells that contain 1 contaminating parent bacterial cell per 10^7 minicells (see Table 9, col. 234), therefore such a preparation of isolated intact minicells disclosed by Sabbadini et al is interpreted free of any contaminant. In view of foregoing it is clear that Sabbadini teaches the use of isolated intact minicells for delivery of nucleic acid , wherein isolated intact purified minicell is free of contaminants (table 9, example 17 and claim 1) and thus would anticipate the claimed invention.

With regard to applicants' argument that Sabbadini et al fail to teach bringing bispecific ligand into contact with any minicell (see page 6, para. 3-4), it should be noted that bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively. In this regard, contrary to applicants' assertions, Sabbadini et al teach contacting a mammalian cell with a bacterial minicells comprising an active agent such as nucleic acid that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It should be noted that the antibody is covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand disclosed by Sabbadini et al comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively (limitation of claims 11 and 15).

With regard to applicants' argument that Sabbadini et al teach use of plurality of different minicell and therapeutic agents, it should be noted that the disclosure of other embodiments in Sabbadini et al does not negate the fact that cited art specifically teaches the claimed elements. Applicants have not provided any evidence on record as to why the delivery of different molecules are not enabling. The claimed composition in the method appears to be structurally and functionally similar.

Applicants argue that the teachings of Sabbadini are not well-delineated (see page 6). , Applicants further argue that conventional wisdom held that large particles like intact bacterially derived could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis (see page 7). Applicants cite the multiple references (see page 17) to support their argument. Applicants assert that the clathrin-coated pits resemble a cup that envelopes the vector, but the size of the cup is understood to be a limiting factor. Clathrin-coated pits have a limited size of 85-110 nm, due to the size of the clathrin coat. Applicants cite Swanson & Watts, 1995 to support the assertion that minicells are at least 400 nm in diameter. Hence, the skilled artisan would not have expected this targeting approach to work for minicells. Applicants further argue that specific investigations into the effect of particle size on receptor-mediated endocytosis showed the process to be strongly size-dependent (see Dransi and COssart, 1998 and Simones , 1999) (see page 8 of the argument).

In response, it is noted that like instant specification, Sabbadini et al teach an isolated minicell that is broadly interpreted to be a purified minicell free of contaminants capable of delivery of molecules to a target cells. Sabbadini et al teaches same method steps as claimed using similar composition. Applicants should noted that Sabbadini et al teach contacting target non-phagocytic tumor cells with minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). Additionally, it is also disclosed that the method results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Furthermore, tumor cells disclosed by Sabbadini et al meets the structural limitations of "a mammalian cell surface capable of activating receptor mediated endocytosis" "because it is capable of providing the intended use limitation "receptor mediated endocytosis ". In response to applicant's argument that large particles like intact bacterially derived could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, and then it meets the claim. One of ordinary skill in the

art based on the teachings of the specification would conclude that the target non-phagocytic cells disclosed in the method of Sabbadini et al would serve the purpose as claimed.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., size of minicell diameter) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Applicants may wish to amend the claims to limit the bacterially derived intact minicells to a "specific size" in order to distinguish minicells of claimed method from the one known in prior art.

Applicants further argues that Sabbadini, in the cited section example 19 advocates using protoplast and targeting via expression of antibody fusion constructs and effecting uptake (See 9).

Such is found not persuasive because the applicants' fails to provide any evidence that sufficiently support this assertion. Applicants have further engaged in selective reading of the teachings of Sabbadini et al. to formulate the grounds for not teaching the non-phagocytic cells. Contrary to applicants' assertion Sabbadini et al teach tumor cells that are engulfed by isolated minicells by receptor mediated endocytosis in a manner similar to one with macrophage (for example). Furthermore, human cancer cells (A431 cells) are known to be non-phagocytic. Additionally, it is known in prior art that all mammalian cells are endocytosis-competent and thus would also be inherent in the human cancer cells taught by Sabbadini. In fact, Sabbadini et al teach contacting target non-phagocytic tumor cells with minicells containing nucleic acid operably linked to regulatory sequence coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing nucleic acid into the tumor cell (see column 171, col. 1, line 62-65). MPEP 2164.01[R5] states "[A]ny part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein. In the instant case, Sabbadini teach the claimed method step and also disclose method to isolate composition "containing fewer than about 1 contaminating parent bacterial cell per 10^7 minicells" (see Table 9, col. 234) and such a preparation of minicells

disclosed by Sabbadini et al was generally free of any contaminant. Therefore, rejection is maintained for the reasons of record.

Maintained- Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957) for the reasons of record.

Claims are directed to a targeted gene delivery method that comprises bringing bispecific ligands into contact with (a) bacterially derived minicells that contain a therapeutic nucleic acid sequence and (b) non-phagocytic mammalian cells, such that (i) said bispecific ligands cause said minicells to bind to said mammalian cells and (ii) said minicells are engulfed by said mammalian cells, which produce an expression product of said therapeutic nucleic acid sequence. Claim 3 limits the method of 1 wherein said bispecific ligand comprises polypeptide or carbohydrate and wherein said bispecific ligand comprises a first arm that carries specificity for a bacterially derived minicells surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor. Claim 5 is method according to claim 3, wherein first and second arm are multivalent and wherein said minicell surface structure s an O-polysaccharide component of a liposaccharide on minicell cell surface.

With respect to claims 1, 3, Sabbadini et al. teach a gene delivery method comprising contacting a target mammalian cell with a bacterial minicells containing a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of the target mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It is also disclosed that the active agent is a nucleic acid (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66) and the target mammalian cell may include cos or A-431 cancer cell line that are non phagocytic mammalian cell (column 252, line 30 and 55). Sabbadini et al. teach that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material in the target cell (see col. 164, lines 28-37). Furthermore, Sabbadini et al teach attaching binding compounds-or moieties to minicells via membrane proteins that are displayed on the minicells. The compound to be conjugated to the minicells can be a polypeptide. It is also

disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66). It is also disclosed that the minicells containing genetic material targets cells by using either receptor mediated endocytosis or phagocytosis (col. 159 lines 4-6, 38, line 18).

Although, Sabbadini et al. teach a method of gene delivery by covalently attaching binding moieties including antibody to minicells via membrane proteins that binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that the first arm binding to minicell surface is an O-polysaccharide component of LPS or first and second arm are multivalent.

However, prior to instant invention, Nettelbeck et al teach a recombinant antibody as a molecular bridge, linking the adenovirus capsid to the endothelial cell surface protein endoglin, for vascular targeting of adenoviruses (abstract). It is noted that Nettelbeck et al also disclose a method to construct bispecific single chain diabody directed against endoglin and the adenovirus knob domain (see 885, col.1, para.4). It is also disclosed that the ScFv C4 (endoglin) and the neutralizing anti-knob scFv S11 are combined in a single-chain diabody (scDb EDG-Ad) (see figure 3) for experimental analysis. Nettelbeck et al reported enhanced adenoviral infectivity mediated by scDb EDG-Ad that was restricted to endoglin-positive cells showing cell specific targeting (see figure 6, page 889, col. 2, para. 2).

Although Nettelbeck et al describes the advantage of using single chain diabody to target adenoviral fiber knob domain to endoglin expressing cancer cell, but differed from claimed invention by not disclosing first arm specific to O-polysaccharide of a LPS.

Prior to instant invention, Coldwell et al teach production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide (LPS) (abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Nettelbeck et al and Coldwell by using an single chain dibody (bivalent bispecific antibody) to bring together intact minicell and mammalian cell such that minicell binds to mammalian cell and minicell that are engulfed by the mammalian cell with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to use an antibody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for gene transfer by attaching a bacterial minicells with an antibody that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those of Nettelbeck and Coldwell would have resulted in specific gene transfer into endoglin positive endothelial cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

Applicant arguments filed September 17, 2009 have been fully considered but are found not persuasive. Applicant's arguments all rely on the teaching of Sabbadini et al that have been discussed in the preceding section.

Applicants cite a number of papers showing different mechanism used by viruses and liposome that are capable of breaching endosomal membrane thereby allowing escape of endosomal content into the cytoplasm. Applicants assert that skilled artisan had no basis to have expected the content of minicell vector to escape lysosomes and avoid degradation. Applicants argue that instant specification teaches that minicells that carry sufficient copy of plasmid DNA in minicells also can escape lysosomal degradation (see page 11 and 12 of the argument). Applicants then describe how viruses use several strategies to overcome nuclease activity and low movement within cytosol. Applicants further argue that skilled artisan would have not expected the transport of nucleic acid to the mammalian nucleus, where expression of encoded product occurs. Applicants cite multiple references to show that viruses have developed several strategies for delivering nucleic acid (see page 13 and 14 of the argument). Applicants' ague that Sabbadini contains nothing more than unsubstantiated suggestions that lacks working examples of targeted gene delivery. In this regard, applicant notes that his work recently captured the cover of the prestigious journals (see page 15).

Such is found not persuasive because different mechanism used by viruses and liposome for breaching endosomal membrane is irrelevant to the pending claims. In the instant case, base claim require bringing bispecific ligands into contact with (a) intact bacterially derived minicell that contains nucleic acid operably linked to a promoter and (b) non-phagocytic mammalian cell. Sabbadini et al specifically teach contacting a mammalian cell with a bacterial minicells comprising a nucleic acid under the control of a promoter, wherein the surface of the minicell is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It should be noted that the antibody is covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand disclosed by Sabbadini et al comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively and

wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (see column 7, line 1-12 and col. 17, 6-15, col. 136, lines 58-66). It is further disclosed that the receptor/ligand interaction will result in the endocytosis of the minicell into the target cell where the minicell would release and deliver the genetic material (see col. 164, lines 28-37).

It is relevant to point out that Sabbadini et al also teach other strategies that included a minicell that may express a protein such as invasion to induce receptor mediated endocytosis (Pepe et al., " Proc. Natl. Acad. Sci. U.S.A. 90:6473 6477, 1993 without relying for rejection that interacts with the Beta2 Integrin protein and causes it to dimerize. Upon dimerization the Beta2 Integrin signals for an endocytotic event (see col. 159, lines 5-24). Further as stated in MPEP 716.07, every patent is presumed valid (35 U.S.C. 282), and that presumption includes the presumption of operability (*Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C. Cir. 1935). To the extent, Sabbadini et al teach using minicell comprising nucleic acid similar to one disclosed in the instant application for the transfection, it is reasonable to state that the method of using minicell disclosed by Sabbadini et al is enabling.

Additionally, with respect to applicants' submission that it was unexpected to deliver gene from a minicell and the ability of minicells to deliver gene and destabilization of minicell integrity, it is emphasized that the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that the specific limitations and conditions as set forth in argument is *effective* in delivering the gene to a target cells. A person of skill in the art would have been motivated to use an single chain antibody diabody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent including nucleic acid as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for targeted delivery of gene by attaching an antibody to a bacterial minicells that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those in

Nettelbeck and Coldwell would have resulted in specific targeted gene transfer into endoglin positive target mammalian cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Withdrawn-Double Patenting

Claims 1-10, 12-18 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28, 48-54 of copending Application No. 12/053,197. Claims 28, 48-54 have been canceled in '197, rendering rejections of claims 1-10, 12-18 moot.

Claims 1-10, 12-18 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-41, 43-47, 48, 50-54 and 73 of copending Application No. 11/765,635. Claims 37-41, 43-47, 48, 50-54 and 73 have been canceled in copending Application No. 11/765,635, rendering rejections of claims 1-10, 12-18 moot.

Maintained-Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 15 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 10/492,301 for the reasons of record.

Claims 1 and 15 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 12/019,090 for the reasons of record.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

While Applicant has requested that the rejection be held in abeyance until allowable subject matter can be identified, a request of abeyance does not overcome or address an issue of obvious double patenting between claims 1 and 15 of the instant case and application '301 and '090. Thus the rejection is maintained.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tomlinson I et al (.Methods Enzymol, 2000, 326, 461-479) teach a method for generating multivalent and bispecific antibody fragments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
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